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A Combined Analysis of D22S278 Marker Alleles in Affected Sib-Pairs: Support for a Susceptibility Locus for Schizophrenia at Chromosome 22q12

Schizophrenia Collaborative Linkage Group (Chromosome 22)*

Michael Gill, Homero Vallada, David Collier, Pak Sham, Peter Holmans, Robin Murray, Peter McGuffin, Shin Nanko, Mike Owen

Department of Psychological Medicine, Institute of Psychiatry (M.G., H.V., D.C., P.S., R.M.), London, Department of Psychological Medicine, University of Wales College of Medicine (P.H., P.M., M.O.), Cardiff, United Kingdom; Department of Psychiatry, Teikyo University, Tokyo, Japan (S.N.)

Stylianos Antonarakis, David Housman, Haig Kazazian, Gerald Nestadt, Ann E. Pulver

University of Geneva, Geneva, Switzerland (S.A.); Massachusetts Institute of Technology, Boston, Massachusetts (D.H.), University of Pennsylvania, Philadelphia, Pennsylvania (H.K.), Johns Hopkins University, Baltimore, Maryland (G.N., A.E.P.)

Richard E. Straub, Charles J. MacLean, Dermot Walsh, Kenneth S. Kendler

Department of Human Genetics and Psychiatry, Medical College of Virginia, Richmond, Virginia (R.E.S., C.J.M., K.S.K.); St. Lomans Hospital, Dublin, Ireland (D.W.)

Lynn DeLisi, Mihael Polymeropoulos, Hilary Coon, William Byerley, Ray Lofthouse, Elliot Gershon, Lynn Golden, Timothy Crow

Department of Psychiatry, SUNY Stony Brook, Stony Brook, New York (L.D., M.D., R.L.), University of Utah, Salt Lake City, Utah (H.C., W.B.); Clinical Research Centre, Harrow, United Kingdom (T.C.) Clinical Neurogenetics Branch, NIMH Bethesda, Maryland (E.G., L.G.)

William Byerley, Hilary Coon, Robert Freedman

Department of Psychiatry, University of Utah Medical School, Salt Lake City, Utah (W.B., H.C.); University of Colorado Health Sciences Centre, Denver, Colorado (R.F.)

Claudine Laurent, Sylvie Bodeau-Pean, Thierry d'Amato, Maurice Jay, Dominique Campion, Jacques Mallet

Laboratoire de Genetique Moleculaire de la Neurotransmission et des Processus Neurodegeneratifs, Centre National de la Recherche Scientifique, Paris, France

Dieter B. Wildenauer, Bernard Lerer, Margot Albus, Manfred Ackenheil, Richard P. Ebstein, Joachim Hallmayer, Wolfgang Maier

Psychiatric Hospital, University of Munich, Munich (D.B.W., M.Ac., J.H.), State Mental Hospital, Haar (M.Al.), Psychiatric Hospital, University of Mainz, Mainz (W.M.), Germany; Hadassah-Herzog Psychogenetics Program, Jerusalem, Israel (B.L., R.P.E.)

Hugh Gurling, David Curtis, Gusharon Kalsi, Jon Brynjolfsson, Thordur Sigmundson, Hannes Petursson

University College London Medical School, London, United Kingdom (H.G., D.C., G.K.) Department of Psychiatry, Borgarspitalinn, Reykjavik, Iceland (J.B., T.S., H.P.)

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*The study was coordinated by Michael Gill, Homero Vallada, and David Collier.

Address reprint requests to Homero Vallada, Institute of Psychiatry, DeCrespigny Park, Denmark Hill, London SE5 8AF, United Kingdom.

Douglas Blackwood, Walter Muir, David St. Clair, Lin He, Susan Maguire

MRC Human Genetics Unit, Western General Hospital, Department of Psychiatry, Royal Edinburgh Hospital, Edinburgh, Scotland (D.B., W.M., D.St.C., L.H., S.M.)

Hans W. Moises, Hai-Gwo Hwu, Liu Yang, Claudia Wiese, Li Tao, Xiehe Liu, Helgi Kristbjarnason

Molecular Genetics Laboratory, Department of Psychiatry, Kiel University Hospital, Kiel, Germany (H.W.M., C.W., L.Y.); Department of Psychiatry, National Taiwan University Hospital, Taiwan, (H.-G.H.); Department of Psychiatry, West China University, Chengdu, Peoples' Republic of China (L.T., X.L.); Department of Psychiatry, National University Hospital, Reykjavik, Iceland (H.K.)

Douglas F. Levinson, Bryan J. Mowry, Helen Donis-Keller, Nicholas K. Hayward, Raymond R. Crowe, Jeremy M. Silverman, Derek J. Nancarrow, and Christina M. Read

Department of Psychiatry, Medical College of Pennsylvania and Hahneman University, Philadelphia, Pennsylvania (D.F.L); University of Queensland, Brisbane, Australia (B.J.M., D.J.N); Department of Surgery, Washington University School of Medicine, St. Louis, Missouri (H.D.-K, C.M.R.); Queensland Institute of Medical Research, Brisbane, Australia (N.K.H., D.J.N.); Department of Psychiatry, University of Iowa Hospitals and Clinics, Des Moines, Iowa (R.R.C.); and Department of Psychiatry, Mt. Sinai School of Medicine, New York (J.M.S.) (USA/Australia Schizophrenia Linkage Consortium)

Several groups have reported weak evidence for linkage between schizophrenia and genetic markers located on chromosome 22q using the lod score method of analysis. However these findings involved different genetic markers and methods of analysis, and so were not directly comparable. To resolve this issue we have performed a combined analysis of genotypic data from the marker D22S278 in multiply affected schizophrenic families derived from 11 independent research groups worldwide. This marker was chosen because it showed maximum evidence for linkage in three independent datasets (Vallada et al., Am J Med Genet 60:139–146, 1995; Polymeropoulos et al., Neuropsychiatr Genet 54:93–99, 1994; Lasseter et al., Am J Med Genet, 60:172–173, 1995. Using the affected sib-pair method as implemented by the program ESPA, the combined dataset showed 252 alleles shared compared with 188 alleles not shared (chi-square 9.31, 1df, P = 0.001) where parental genotype data was completely known. When sib-pairs for whom parental data was assigned according to probability were included the number of alleles shared was 514.1 compared with 437.8 not shared (chi-square 6.12, 1df, P = 0.006). Similar results were obtained when a likelihood ratio method for sib-pair analysis was used. These results indicate that may be a susceptibility locus for schizophrenia at 22q12.

KEY WORDS: linkage analysis, sib pair analysis, functional psychosis, candidate locus

INTRODUCTION

Recently Pulver et al. [1994a], as part of a genome wide search, identified a region on the long arm of chromosome 22 that shows some evidence for linkage to schizophrenia. However the maximum lod score was not high (Zmax = 1.54) and heterogeneity tests were inconclusive. To investigate this finding a multicenter study was performed using 217 families from three separate groups using the markers D22S268, IL2RB, and D22S307 [Pulver et al., 1994b]. The overall lod scores from this replication study were substantially negative and did not support the original findings.

However, during a systematic linkage study of chromosome 22, Vallada et al. [1995] found the best evidence for linkage (Z max = 1.51 at θ = 0.1) with the marker D22S278, located between D22S268 and IL2RB. More recently a sib-pair analysis of the Pulver et al. [1994a] data was reported [Lasseter et al., 1995]. This demonstrated excess sharing for a range of 22q markers including D22S278, which showed the strongest evidence for linkage.

In addition to the findings of Pulver et al. [1994a] and Vallada et al.[1995], Coon et al. [1994b] reported a lod score of 2.09 at θ = 0.1 for a recessive genetic model with the marker D22S276, which is located 15 cM telomeric to D22S278. In their data, D22S278 produced a lod score of 0.69 at θ = 0.2. A fourth independent study, by Polymeropolous et al. [1994], reported a maximum lod score of 0.37 at θ = 0.2 for marker D22S278, using data from affected pedigree members only. In addition, using an affected sib-pair method, they found greater than expected allele sharing for markers D22S278, D22S281 (located 4 cM centromeric of D22S278), D22S283 (3 cM telomeric), and D22S279 (13 cM telomeric). Finally, Schwab et al. [1995] reported excess sharing of alleles (P = 0.07) for marker D22S304 which is 3.5 cM centromeric to D22S278.

In summary, a number of groups have recently reported positive linkage findings on chromosome 22 but these are neither confined to a single locus nor to a specific method of analysis. Although the different genetic parameters used by each group for a lod score analysis may be resolved for the purposes of a combined analysis, there may be real differences in the modes of transmission between geographically disparate pedigree samples, making the comparison of lod score data problematic.

The detection of a gene causing disease in a small proportion of families, or contributing in a minor way to susceptibility in all families, may not be possible in a single dataset. However, in attempting to combine data from a number of centres, bias may occur through the preferential selection of groups with positive findings. In order to avoid this it is imperative to analyse data from as many groups working in the field as possible. To facilitate this, it is necessary that the diagnostic, laboratory, and statistical procedures be as simple and *robust as possible.*

A suitable method of statistical analysis is the affected sib-pair method, a non-parametric alternative to the lod score method. It does not require specification of the genetic model and is capable of detecting genes of minor effect. It has been employed with success in complex genetic diseases including diabetes [Spielman et al., 1989], atopic eczema [Moffat et al., 1992], and Alzheimer's disease [Bailey-Wilson and Bamba, 1993]. In the present study, we have conducted a combined analysis of data from 11 centres for the marker D22S278 using the affected sib-pair method. This marker was chosen because it showed maximum evidence for linkage in three independent datasets [Vallada et al., 1994; Polymeropolous et al., 1994; Lasseter et al., 1994] and it maps between D22S268 and IL2Rβ, two of the three markers used in the Pulver et al. study [1994b].

METHODS

All centres known to us to be involved in linkage analysis of schizophrenia using DNA markers were contacted and invited to participate in the study. It was decided in advance to use a narrow definition of the disease phenotype, i.e., schizophrenia and schizoaffective disorder as defined by DSMIIIR [American Psychiatric Association, 1987] or RDC [Spitzer et al., 1978]. All diagnostic information was obtained using well known and robust diagnostic instruments. Data were transferred to the Institute of Psychiatry and Cardiff, usually by email, in the "linkage file" format. A summary of the pedigrees and diagnostic procedures of each participating group is presented in Table I. Further details are available in the references to previous work by the individual groups.

ESPA Analysis

Affected sib-pair analysis was conducted using two methods: the Extended Sib-Pair Analysis (ESPA) program [Sandkuijl, 1989] and a likelihood method [Holmans, 1993]. The ESPA program makes two calculations. The first scores the proportion of alleles identical by descent (IBD) in affected sib-pairs where parental genotypes are known. The second estimates the proportion IBD for sib-pairs whose parental or sibling genotype is unknown, by considering all possible parental or sibling genotypes and their relative likelihoods as determined by the specified allele frequencies using the MLINK routine [Lathrop et al., 1984]. In this study allele frequencies were calculated from unrelated individuals in the pedigree sets and each set analysed separately. In both cases a test for linkage is based on a one-tailed chi-squared test of whether the proportion of alleles IBD is greater than 50%, the expected value under no linkage. In ESPA, affected sib-pairs in sibships with three or more affected members are treated independently.

Likelihood Ratio Method for Sib-Pair Linkage Analysis

This method, introduced by Risch [1990], gives a powerful test of linkage for incompletely polymorphic markers and/or missing parental data. The idea is to express the likelihood of the observed marker data in each sibship as a linear combination of the (unknown) IBD sharing probabilities Z (Z0, Z1, and Z2) of the affected pair, where the coefficients are functions of the marker allele frequencies. The likelihood of the whole sample can be maximised with respect to Z via the EM algorithm, and a likelihood ratio test performed by dividing this maximised likelihood by its value under the hypothesis of no linkage Z = (1/4, 1/2, and 1/4), the results being presented as lod scores.

Holmans (1993) showed that the power of the method could be increased further by restricting maximisation to the set of Z corresponding to possible genetic models, that is, $Z1 \leq 0.5$ and $2Z0 \leq Z1$. Test criteria under this restricted maximisation may be found in Holmans [1993]. The method deals with sibships containing

TABLE 1. Summary of the Pedigrees From Each Centre and References for Further Information

Group	Number of pedigrees	Average number of affected/family	Diagnostic criteria used	Reference for further details
Institute of Psychiatry Cardiff	23	3.3	RDC	Gill et al. [1993]
Johns Hopkins University (JHU)/MIT	58	2.2	DSMIII-R	Pulver et al. [1994a]
Medical College of Virginia (MCV)	258	2.4	DSMIII-R	Su et al. [1993]
National U.S.A/Clinical Research Centre, Harrow	71	2.3	DSMIII-R	Polymeropolous et al. [1994]
University of Utah/University of Colorado	9	4.0	RDC	Coon et al. [1994a]
C.N.R.S., Paris	46	2.8	DSMIII	Campion et al. [1994]
Jerusalem/Mainz/Munich/Haar	30	2.7	RDC	Schwab et al. [1994]
University College Hospital(UCH)	23	3.4	RDC	Kalsi et al. [1994]
Edinburgh	10	3.7	RDC	St. Clair et al. [1989]
Kiel University Hospital	18	2.4	DSMIII-R	Hwu et al. [1988]
USA/Australia	28	2.1	DSMIII-R	Levinson and Mowry [1991]

more than two affected siblings by considering each possible affected pair and weighting the contribution of such pairs by 2/n, where n is the number of affected siblings. This is the correction advocated by Suarez and Hodge [1979].

Heterogeneity

Heterogeneity between datasets was assessed by a chi-square test of homogeneity and by an "admixture" model likelihood method. Both methods are based on the proportions of alleles IBD in the individual datasets, in fully known pairs from the ESPA output. The chi-squared test examines whether the proportion of alleles IBD is the same for all datasets, irrespective of whether this proportion is 50%. The "admixture" model, generally used to measure heterogeneity across families is used here to assess heterogeneity of results between centres. The model assumes that a proportion (alpha) of the datasets show increased IBD, while the others (1 - alpha) do not. The likelihood is evaluated at different values of alpha and proportion IBD; and a test for "admixture" is obtained by comparing the maximum likelihood to the likelihood at alpha = 1, i.e., that all datasets show increased IBD.

RESULTS

Table II shows the number of alleles at D22S278 shared and not shared for each group separately and for the combined dataset. For fully genotyped sets of affected sib-pairs and their parents (n = 296), the combined dataset shows 252 alleles shared compared with 188 alleles not shared (chi-square = 9.31, 1df, $P = 0.001$). For the sib-pairs where parental data is assigned according to probability (n = 324) the data shows 262.1 alleles shared compared with 249.8 not shared (chi-square = 0.30 df = 1, $P = 0.3$). For the total sib-pairs (n = 620) the number of alleles shared is 514.1 compared with 437.8 not shared (chi-square = 6.12, 1df, $P = 0.006$).

Using the likelihood method, the 191 sibships (containing 296 sib-pairs) with both parents typed gave IBD sharing probability estimates of Pr(0) = 0.18, Pr(1) = 0.5, and Pr(2) = 0.32, yielding a log likelihood ratio of 1.55 ($P = 0.007$). When the whole sample was analysed (436 sibships) the sharing probability estimates were Pr(0) = 0.19, Pr(1) = 0.5, and Pr(2) = 0.31. The log likelihood ratio was then 1.79 ($P = 0.004$). The sharing probability estimates are very similar for both samples, suggesting that the results are not being bi-

TABLE II. Sib-Pair Analyses for the Marker D22S278*

Group	Total number of sib-pairs	ESPA method Number of alleles		LIKELIHOOD method I.B.D.** sharing probability estimates		
		Shared	Not shared	Pr(0)	Pr(1)	Pr(2)
Institute of Psychiatry	a. 14	c. 17	c. 6	c. 0.08	c. 0.50	c. 0.43
(IOP) / Cardiff	b. 45	d. 37.95	d. 27	d. 0.15	d. 0.50	d. 0.35
John Hopkins	34	32	17	0.20	0.39	0.41
University / MIT	51	47.96	23	0.16	0.37	0.47
Medical College	31	22	21	0.23	0.50	0.27
Virginia (MCV)	177	147.86	147.14	0.246	0.50	0.254
National U.S.A./	82	69	60	0.22	0.50	0.28
CRC Harrow	100	83.85	66	0.19	0.48	0.32
University of Utah/	15	11	5	0.16	0.50	0.34
University of Colorado	20	15.37	9	0.11	0.50	0.39
CNRS, Paris	24	21	14	0.25	0.49	0.26
	66	53.35	48.67	0.23	0.46	0.30
Jerusalem/Mainz/	39	28	23	0.16	0.50	0.34
Munich/Haar	43	33.00	26	0.16	0.50	0.34
University College	10	6	8	0.25	0.50	0.25
Hospital (UCH)	48	33.33	39	0.25	0.50	0.25
Edinburgh	22	17	15	0.23	0.46	0.32
	23	17.67	15	0.22	0.43	0.35
Kiel University	10	11	8	0.10	0.50	0.40
Hospital	17	15.54	13	0.13	0.50	0.37
U.S.A./Australia	20	18	11	0.16	0.50	0.34
	36	28.21	24	0.16	0.50	0.34
Total	a. 296	c. 252	188[1]	c. 0.18	0.50	0.32[3]
	b. 620	d. 514.1	437.8[2]	d. 0.19	0.50	0.31[4]

*For details of each group, refer to Table I. "Total number of sib-pairs" in column two indicates the number of complete (a) or partial (b) sib-pairs based on the number of DNA samples available for genotyping. In columns 3–7 under "ESPA Method" and "LIKELIHOOD method" the data is classified according to whether it is derived from fully known only (c) or fully known *and* partially known (d) sib-pairs (see text).

[1] Chi-square (shared/not shared) = 9.31 (df = 1), $P = 0.001$.

[2] Chi-square (shared/not shared) = 6.12 (df = 1), $P = 0.006$.

[3] Lodscore = 1.55 ($P = 0.007$).

[4] Lodscore = 1.79 ($P = 0.004$).

** I.B.D., Identical by Descent.

TABLE III. Division of ESPA Results According to Number of Affected Individuals in Each Sibship

	ESPA (completely known parents only)		
	Shared	Not shared	Chi-Square
Pairs	118	88	4.37 (P = 0.018)
Trios	51	34	3.40 (P = 0.033)
Quadruplets	63	46	2.65 (P = 0.052)
Quintuplets	6	4	(n.s.)
Sextuplets	14	16	(n.s.)

ased by incorrect assignment of missing parental data. Table III shows the proportions of alleles shared and not shared for the sample by the number of affected in the sibship, showing that the excess of sharing is not confined to large sibships.

The chi-squared test for homogeneity gave no evidence that the proportion IBD differed significantly between datasets (chi-squared = 8.04, df = 10, P = 0.62). Similarly, the maximum of the likelihood surface occurred at alpha = 1 and proportion IBD = 0.58, again suggesting that the observed differences in proportion IBD between datasets are random sampling fluctuation rather than real.

DISCUSSION

The aim of this study was to clarify the significance of findings, derived from independent studies, suggestive of linkage between polymorphic markers on chromosome 22 and schizophrenia. These studies were neither restricted to a single marker nor obtained by easily comparable methods of analysis. Therefore we judged it necessary to apply a robust, non-parametric method of analysis of data from a single marker, to all datasets, using compatible diagnostic procedures. The non-parametric affected sib-pair method was chosen, and the affected phenotype was defined as schizophrenia or schizoaffective disorder.

The most robust result of the ESPA analysis using fully known sibships shows a significant excess of alleles shared by affected individuals (chi-square = 9.31, df = 1, P = 0.001). The strength of this finding was deflated when partially known sibships were included in the analysis (chi-square = 6.12, df = 1, P = 0.006). However, since reconstruction of the unknown parental genotypes is uncertain and dependent on the correct specification of gene frequencies, more emphasis should be given to the results from the "fully known" affected pairs.

Of the two methods of analysis used, ESPA gave more significant results than the likelihood method when both parents were typed. This difference may be because the likelihood method applies the Suarez correction [Suarez and Hodge, 1979] to pairs taken from multiply affected sibships, whereas ESPA does not. This makes ESPA more powerful when the data contains multiply-affected sibships (as was the case here) provided genotyping information is available for both parents. However, when siblings with missing parental data were included, there was little difference in the significance levels and, if anything, the results of likelihood method were slightly more significant.

We are not able to exclude homogeneity in these families for this set of marker data by either chi-square or admixture model tests. This lack of evidence for heterogeneity between datasets from different centres may indicate that there is a small increase in the proportion IBD in affected pairs in all populations from which samples were drawn. However, we cannot exclude the possibility that this locus has a major effect in some families. In either case, although it is reasonable to consider possible heterogeneity between centres, such a division of data may not fully reflect the ethnic origin of the families. Some groups have obtained their families from more than one geographic location, and even within a single geographic location families may not share the same ethnic background, making such an analysis problematic.

A possible source of bias in this combined analysis is the preferential inclusion of datasets with positive findings, either because we are more likely to be aware of them, or because groups with promising preliminary findings are more enthusiastic about participation. We have attempted to avoid this bias by including what we believe to be all of the larger datasets available worldwide. We decided to perform this combined analysis on the basis of suggestive sib-pair and lod score analyses for the marker D22S278 [Vallada et al., 1994; Coon et al., 1994b; Polymeropolous et al., 1994] and an awareness of linkage results for other markers near D22S278 from JHU/MIT [Pulver et al., 1994a; Lasseter et al., 1994], UCH [Kalsi et al., 1994], and MCV [Pulver et al., 1994b]. At the onset of this analysis, D22S278 had not been typed in the datasets from Jerusalem/Mainz/Munich/Haar, Kiel, CNRS, Edinburgh, and U.S.A./Australia. These datasets can therefore be considered an independent replication sample. Analysis of fully known sib-pairs in this sample shows 95 alleles shared compared with 71 alleles not shared (chi-square 3.47, df = 1, P =0.03).

Overall, our results are suggestive of a susceptibility locus for schizophrenia near to the D22S278 locus on chromosome 22. The majority of datasets show a small excess of alleles IBD among affected siblings, and the effect is not different between small and large sibships (Table III) suggesting that the locus may exert an effect throughout the sample rather than being major disease causing locus in a few large high density families. The susceptibility locus may be neither necessary nor sufficient [Greenberg, 1993] for the development of schizophrenia, but instead act to increase risk in an additive or multiplicative fashion when combined with other genetic loci and environmental effects.

What is the likely magnitude of the contribution of this locus to the overall liability to develop schizophrenia? Suarez et al. [1978] have derived the relationship between the excess in proportion IBD and the parameters of a single locus model: Kp (prevalence), Va (additive genetic variance), Vd (dominance genetic variance), and θ (recombination fraction). Assuming that Kp = 0.01, θ = 0.01, and the absence of dominance (Vd = 0), it can be shown that for this locus, Va constitutes about 1% of the total variance in liability to develop

schizophrenia (which is Kp (1 - Kp)). If θ is assumed to be 0.1, then the estimate of Va rises to 2%. Clearly, these estimates are approximate and dependent on a number of uncertain and simplistic assumptions, but they do indicate that a susceptibility gene for schizophrenia at or near D22S278 is likely to account for only a small proportion of the total genetic component of the disease.

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